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03 April 2002

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04/03/02

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Attorney Docket No. P50572X1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: DeBouck, *et al.*

03 April 2002

Serial No.: 09/297,701

Group Art Unit No.: 1655

Filed: May 5, 1999

Examiner: Souaya, J.

For: METHODS FOR IDENTIFYING GENES ESSENTIAL TO THE
GROWTH OF AN ORGANISM

Assistant Commissioner of Patents
Washington, D.C. 20231
Attention: Box AF

AMENDMENT & RESPONSE UNDER 37 C.F.R. §1.114

In response to the Advisory Action mailed March 6, 2002 (Paper No. 15)
(herein "Advisory Action"), the Applicants respectfully request entry into the record,
and consideration of this response. As this amendment and response is timely filed
within the shortened statutory period for response of 3 months and with a Petition for
a Three-Month Extension of Time and payment of the appropriate fee. Please charge
any additional requisite fees relating to this amendment and response to Deposit
Account No. 19-2570.

Please amend the above-identified application as follows:

In the Claims:

Please amend Claims 1 and 12 as follows:

04/15/2002 AMENDMENT 00000150 192570 09257701

02 FC:117 920.00 CH

1. (Thrice Amended) A method of identifying genes essential to growth of a single celled organism comprising:
- (a) preparing a genomic library of the single celled organism;
 - (b) providing a plurality of identical grids, each grid comprising a surface on which is immobilized at predefined regions on said surface a plurality of defined materials derived from the genomic library;
 - (c) mutagenizing the single celled organism by transfection with (i) a randomly integrated transposon or a similar insertional or transposable element of known sequence or (ii) with a constructed suicide vector;
 - (d) growing a test culture comprising the mutagenized single celled organisms and a control culture comprising non-mutagenized single celled organisms under a set of defined conditions;
 - (e) harvesting surviving cells from the cultures;
 - (f) extracting and isolating DNA from harvested cells of the test culture;
 - (g) extracting and isolating RNA or DNA from harvested cells of the control culture;
 - (h) generating labeled polynucleotide probes wherein an oligonucleotide primer extension reaction directed against (i) the randomly integrated transposon or similar insertional or transposable element of known sequence or (ii) the constructed suicide vector, and the reaction extends into flanking genomic DNA;
 - (i) generating labeled polynucleotide probes from the isolated RNA or DNA of the control culture;
 - (j) hybridizing the labeled probes generated from the isolated DNA of the test culture to a first identical grid to produce a test hybridization pattern;
 - (k) hybridizing the labeled probes generated from the isolated RNA or DNA of the control culture to a second identical grid to produce a control hybridization pattern;
 - (l) comparing the hybridization patterns to identify genes essential for growth in the single celled organism; and

(m) confirming that said identified gene is essential for growth of the single celled organism.

12. (Thrice Amended) A method of identifying genes essential to growth of a single celled organism by identifying conditionally lethal mutant genes, which comprises:

(a) preparing a genomic library of the single celled organism: (i) in an integration vector; or (ii) in an expression vector;

D2 (b) providing a grid comprising a surface on which is immobilized at predefined regions on said surface a plurality of defined materials derived from the genomic library;

(c) mutagenizing the single celled organism by transfection with (i) a randomly integrated transposon or a similar insertional or transposable element of known sequence or (ii) with a constructed suicide vector;

(d) growing the mutagenized single celled organisms under permissive and non-permissive conditions to identify mutagenized single celled organisms containing conditionally lethal mutant genes;

(e) transforming the single celled organism containing said conditionally lethal mutant genes with the genomic library of step (a);

(f) growing the transformed cells under the same non-permissive conditions as step (d) to identify transformed cells in which conditionally lethal mutant genes have been complemented;

(g) harvesting surviving cells;

(h) extracting and isolating DNA from the harvested cells;

(i) generating labeled polynucleotide probes wherein an oligonucleotide primer extension reaction directed against (i) the randomly integrated transposon or similar insertion or transposable element of known sequence or (ii) the constructed suicide vector, and the reaction extends into flanking genomic DNA;

(j) hybridizing the labeled probes generated from the isolated DNA to a grid,
whereby such probes that hybridize to the grid identify genes essential for growth of
the single celled organism.

REMARKS

Claims 1-12 are pending in the instant application. Claims 1-12 stand rejected. No claims have been objected to. Claims 1 and 12 have been amended. Support for the amended claims is on page 10, line 12-15, of the specification. In view of the following amendment and response, the Applicants believe the claims presented herein are allowable. Reconsideration is respectfully requested.

Attached hereto as pages 8 -10 is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

REJECTIONS UNDER 35 U.S.C. §103(a)

Claims 1-12 are rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over a combination of Nishi, *et al.* (JBC, march 1994, vol. 269, pp. 6320-6324)(herein referred to as "Nishi") and Quandt, *et al.* (Gene, 1993, vol. 127, pp. 15-21)(herein referred to as "Quandt") in view of Lennon, *et al.* (Trends in Genetics, October 1991, vol. 7, pp. 314-317)(herein referred to as "Lennon").

The Applicants respectfully traverse this rejection to the extent that it applies to Claims 1-12. "[T]he references must be viewed without the benefit of hindsight vision afforded by the claimed invention." *Hodosh v. Block Drug Co.*, 786 F.2d 1136, 1143 n.5, 220 U.S.P.Q. 182, 187 n.5 (Fed. Cir. 1986). The claimed invention could not have been obvious to one skilled in the art, at the time the invention was made

because neither Nishi, Quandt, nor Lennon teach or suggest the Applicants' invention as claimed in claims 1-12. The present invention is directed to an array method of identifying genes essential to the growth of single celled organisms such as bacteria, viruses, or fungi that are not necessarily dependent on expression of RNA in test samples to identify genes essential for growth. Nishi and Quandt in view of Lennon neither teach nor suggest using DNA containing insertional or transposable elements from test cultures as template for generating specific hybridization probes. The present invention uses labeled DNA to generate unique hybridization probes wherein primer extension reactions are directed against the inserted elements and the reaction extends into the flanking DNA sequence. Only mutant genes containing a randomly integrated transposon or a similar insertional or transposable element of known sequence or a constructed suicide vector will generate probe that will hybridize with the grids.

For a proper obviousness rejection under 35 U.S.C. 103, the Examiner has the burden of establishing *prima facie* with evidence or reasons that, *inter alia*, at the time of the invention, (1) the prior art of record would have suggested or motivated one of ordinary skill in the art to carry out the combination and modification of the prior art as suggested by the Examiner to arrive at the claimed invention, and (2) "the prior art would also have revealed that in so making or carrying out, those of ordinary skill in the art would have a reasonable expectation of success. Both the suggestion [or motivation] and the reasonable expectation of success must be founded in the prior art, not in the appellants' disclosure." *In re Vaek*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991) (citations omitted).

The Office Action points to nothing in the cited references that would impel a modification of the disclosed methods necessary to arrive at the instant invention.

The Examiner alleges that the claimed invention would have been *prima facie* obvious to the ordinary artisan to have generated shorter probes that contained the inserted elements to detect hybridization differences between mutant and wild type strains.

The Applicants agree with the Examiner's acknowledgment that non-specific hybridization results are common complications in general hybridization methods depending on the length of the probe and hybridization conditions. However, the prior art cited does not suggest or motivate one skilled in the art to generate hybridization probes directed against the inserted elements wherein the reaction extends into the flanking DNA sequence.

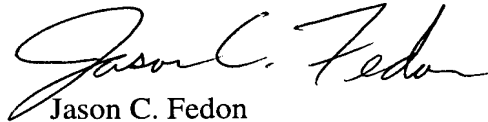
Therefore, it could not have been obvious to one skilled in the art, at the time the invention was made, to make the processes of claims 1-12. Because neither the probe generation nor hybridization method of the invention is taught or suggested by Nishi and Quandt in view of Lennon. "It is impermissible...simply to engage in a hindsight reconstruction of the claimed invention, using the applicants structure as a template and selecting elements from references to fill the gaps." *In re Gormon*, 18 U.S.P.Q. 2d 1885, 1888 (Fed. Cir. 1991) citing *Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985). However, in the interest of advancing prosecution of this case, Applicants have amended Claims 1 and 12 to indicate the reaction [primer extension] extends into the flanking DNA.

The Applicants reserve the right to prosecute, in one or more patent applications, the claims to non-elected inventions, the claims as originally filed, and any other claims supported by the specification. The Applicants thank the Examiner for the Office Action and believe this response to be a full and complete response to such Office Action. Accordingly, favorable reconsideration and allowance of the pending claims is earnestly solicited.

Serial Number: 09/297,701
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If it would expedite the prosecution of this application, the Examiner is invited
to confer with the Applicants' undersigned agent.

Respectfully submitted,



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